No details are yet available about whether the frozen or dried tissue is equally dependent for successful growth on being injected into a mouse of the same genetic constitution. If it were not, there would be good reason for thinking that cell-grafting was no longer wholly the mode of transmission. If it were still necessary, we should have to believe that we were dealing still with grafted cells or else with a virus having a novel type of specificity—not merely for a particular species, but for individuals within that species of a particular constitution ; this would indeed be novel but by no means impossible.

I must mention in passing that some would like to reconcile the virus theory with other theories of cancer by supposing that an inheritable cellular change is always involved, but that in some exceptional instances, as in fowl sarcomata, a self-replicating piece of the altered cell, a plasmagene, or what-you-will, becomes free and able to affect other cells ; that, in fact, a tumour virus when demonstrable is a product of the attacked cell and not an autonomous parasite. This to me is a hypothesis with almost nothing in its favour ; it is gratuitously unnecessary. If there is a free active agent concerned, I prefer to think of it as an honest-to-goodness virus, an independent parasite like other viruses, and I have already tried to show that its properties would not greatly differ from those of other viruses. Heterogenesis, the doctrine that living things may arise from something utterly unlike themselves, as flies from putrid meat, has been propounded again and again ; it has always proved wrong, and will again.

Conclusion

My lecture may have seemed to be arguing, as to its first half, for accepting as feasible the virus theory of cancer and, as to its second half, for doubting a lot of the evidence put forward in favour of that theory. That is not an illogical position. I confess that I should feel, if the virus theory were proved true, that the world was a more orderly place and that all was ready for important advances in the cancer field, going on from the newly consolidated ground. That is the very reason why I feel such an impelling need for confidence that the ground is truly solid and that this can never shift from under our feet. It would be of first-class importance to establish certainly that mouse cancers in general—and not one or two abnormal growths—could be transmitted otherwise than with intact cells. The new techniques Dr. Craigie has described open the way to settling this matter. There are so many things crying out to be done that I am sure we shall learn much more very soon. But—*festina lente !* If I cannot be very positive and dogmatic to-day, let it be remembered that I have been trying to review the present position of the virus theory at a very difficult time, when a new attack on the problem is just being launched.

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AGE OF PUBERTY IN THE TROPICS

BY

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The belief is widely held that children mature earlier in tropical than in temperate climates. This view has not only been repeated by medical authorities but in some instances is reflected in local legislation relating to age of consent and marriage and to the protection of juvenile labour. In actual fact, however, such evidence as exists points to a later rather than an earlier age of menarche (first menstruation) in girls living in tropical areas. No statistical studies of boys appear to have been made. Mills (1937), from a study of the mean age of menarche and the presumptive period of adolescent sterility following the menarche, states: " Sexual maturity in tropical countries comes fully two years later than in the most stimulating temperate regions."

While most recent studies have lent general support to Mills's view that in a tropical climate the menarche is retarded rather than accelerated (Howe, 1939 ; Ito, 1942 ; Kark, 1943), and Ogle (1934) has shown that a hot moist atmosphere may retard sexual maturity in experimental animals when the diet is controlled, it is clear that the available evidence is still rather meagre and much of it open to criticism. This is understandable when it is remembered that in many communities living in tropical areas knowledge of exact age is exceptional and memory of age of menarche correspondingly unreliable. It is also impossible in most instances to assess the relative importance of socio-economic conditions, including diet, and of climate when comparing subjects living in tropical or temperate regions. Heredity, on the other hand, whilst it may affect the age of puberty of the individual, is probably not of major importance when communities of different ethnic stock living under similar social and environmental conditions are compared (Hogben *et al.*, 1948 ; Michelson, 1944).

The following investigation was carried out in Nigeria during the rainy season, July to September, 1949, and comparisons made with figures previously obtained in Great Britain for both girls and boys (Ellis, 1947). The great majority of the subjects included in the study were children born and educated in Lagos, where births have been registrable long enough to allow verification of age ; a smaller proportion were children from mission schools elsewhere in Southern Nigeria whose age was accurately known. None of the children had been out of Nigeria, and no European children were included. Although no attempt has been made to classify the children by tribes, the great majority were Yoraba or Ibo. Since school-children in Nigeria represent a privileged section of the community, it may be assumed that the nutrition of those included in the survey would be above the average of children in the southern provinces generally, where probably less than 20% of girls of school age are in fact attending school.

The Southern Nigerian diet is largely vegetable (yams, cassava, cornflour, plantains, etc.) and includes little meat and practically no milk. Fish, though expensive, is more readily obtainable in Lagos than in most inland areas. Red palm oil, which is widely used, provides a rich source of vitamin A and palm wine of vitamin B complex. A considerable number of the Lagos children were receiving a midday meal at school, which usually meant that groundnuts

and rice were included in the dietary. In only one group of 40 boys included in the survey was there evidence of widespread vitamin B deficiency, as shown by a high incidence of angular stomatitis ; these boys were from a residential mission school where palm wine had been excluded from the diet. In general, the physique and nutrition of the children appeared reasonably good, despite a high incidence of latent malarial infection and the presence of intestinal parasites (principally ascaris).

The township of Lagos, which is situated on a coastal island in latitude 6° 27', approximately 450 miles north of the Equator, has a characteristically tropical climate, though it is not so hot as some inland areas and has a lower rainfall than Calabar. Meteorological conditions are indicated by figures quoted from Quinn-Young and Herdman (1948) : mean maximum shade temperature, 89° F. (31.66° C.) ; mean minimum temperature, 71° F. (21.66° C.) ; mean relative humidity, 79.5% ; annual rainfall, 71.63 in. (181.87 cm.).

Methods

Since puberty represents a series of changes which include alteration of growth-rhythm, endocrine readjustment, and the appearance of secondary sexual characters, taking place over a more or less prolonged period, it follows that attempts to define and compare " the age of puberty " by any single criterion are at best arbitrary. The series of pubertal changes which occur have been discussed in more detail by Greulich et al. (1942), Hogben et al. (1948), and others. Nevertheless, comparisons between comparable groups made on the basis of clearly defined though restricted criteria are of some value if their limitations are recognized.

In the case of girls, the great majority of observers have confined themselves to defining the mean age of menarche (first menstruation), without recording the signs of puberty —e.g., early breast development or appearance of pubic hair —which commonly precede it, or considering the adolescent phenomena—e.g., irregular menstruation or ovulation, adolescent sterility—which may follow it. Where this criterion is used, as in the present study, it must be clearly emphasized that the age incidence of only one manifestation of puberty is being compared, and that no information is offered with regard to the age of attainment of full maturity. In the present study the age of menarche was determined by questioning 300 Nigerian girls aged 17 to 21, the results being shown as a distribution curve representing the percentage menstruating in each year of age. Comparison was made with the information received from 470 nurses in Great Britain, aged 18 years and over (the majority being in training and under 25), this being referred to subsequently as the English series.

Two objections may be raised to this retrospective method of obtaining information. The first, and most important, is that memory is unreliable and that this factor might affect the two groups unequally. This was evident in Kark's (1943) study of Bantu girls, in which she found that older girls tended to give a later age of menarche than younger ones. In the present instance, however, all the girls questioned had been at school at the time of menarche, and random cross-checking of the age given against the child's school class and the season at which menarche had occurred gave general confirmation of the stated ages. Co-operation of the school staff in confirming ages was enlisted, but it was not possible to interview parents. The second objection to the method is that the mean ages of the groups compared may affect the mean ages of menarche ; thus if the survey includes age groups in which less than 100% of girls have already menstruated the mean age of

menarche will be lowered. Cross-checking with a further sample, however, showed that the proportion of girls in the 17 to 18 year age groups who had not reached the menarche was so small that it could be disregarded, and the Nigerian and English series were therefore considered comparable for the present purpose. From the results obtained, both the mean age of menarche and the median age—i.e., the age at which 50% had menstruated and 50% had not —were calculated. These were found to correspond closely, as would be expected with a regular distribution curve.

In order to check the findings a further series of 250 Nigerian girls aged 8 to 18 were examined, and each yearly age group was divided into the percentage non-pubescent (pre-menarche, and showing no evidence of breast development), the percentage pubescent (in which early breast development was present but the menarche had not occurred), and the percentage adolescent (those who had reached the menarche). The age of menarche was determined in the case of the adolescent girls. The number who had reached the menarche by each successive birthday could then be calculated and expressed as a percentage of the total who had passed that age. From these figures the median age of menarche for the group was determined, and could be compared with the median age of menarche of the previous Nigerian series. This method, which was employed by Wilson and Sutherland (1949), has the advantage that in a considerable proportion of cases the menarche will have occurred within one or two years of the time of inquiry, and that the likelihood of error due to faulty memory is correspondingly reduced. It may be noted in this connexion that the menarche is an event of considerable importance in the life of the West African girl, and one unlikely to be readily forgotten.

In the case of boys there is no well-defined point corresponding to the menarche which can be determined retrospectively. The age of onset of puberty was therefore assessed by the examination of yearly age groups. The boys in each age group were graded as non-pubescent, pubescent, or adolescent, and the number of each grade shown as a percentage of the age group. The criteria for these gradings have already been described (Ellis, 1946), and were the same as those used for the control series in Great Britain. Briefly, the grading " non-pubescent " was given when pigmented pubic hair was entirely absent and genital development infantile ; " pubescent " when pigmented pubic hair and/or early but incomplete genital development was present ; and " adolescent " when both growth of pubic hair and genital development were well advanced. Admittedly the classification is arbitrary, since one stage of development passes gradually and not abruptly into the next, but it has been found in practice that the grading serves to distinguish three successive stages of maturity in the great majority of instances. A total of 333 Nigerian boys aged 9 to 18 were examined and compared with a control series of 662 examinations made in Great Britain.

Results in Girls

The figures for the first Nigerian series of 300 girls are shown in parallel with those of the English series of 470 girls, each being expressed as percentages of the total number in the series. The superimposed distribution curves (Fig. 1) show the later occurrence of menarche and the more limited spread of the curve in the Nigerian series. The mean age of menarche in the Nigerian series is 14.22 years and that of the English series is 13.73 ; the difference between the means is 0.49 year, with a standard error of 0.085. Thus the difference is 5.7 times its standard error

TABLE I.—*Percentage Reaching Menarche in Each Year of Age*

Group			Nigeria (300)	Great Britain (470)
9–10 years	..	..	0	0·6
10–11 „	..	..	0	0·9
11–12 „	..	..	1·0	7·5
12–13 „	..	..	8·7	19·1
13–14 „	..	..	32·7	30·6
14–15 „	..	..	35·3	27·4
15–16 „	..	..	20·0	8·5
16–17 „	..	..	2·0	3·6
17–18 „	..	..	0·3	1·3
18–19 „	..	..	0	0·4
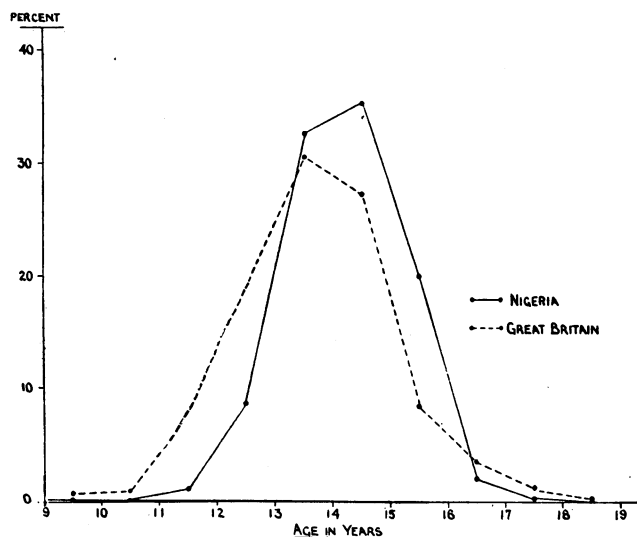
FIG. 1.—Distribution curves of age of menarche (Nigeria and Great Britain).

and may be considered statistically significant. The standard deviation of the English series is 1.37, while that of the Nigerian series is only 1.00, indicating a greater variability in the age of menarche in the English series.

The second Nigerian series was used for calculating the median age of menarche in order to cross-check the results in the first. Table II shows in parentheses the number who had passed each successive birthday and the percentage of these who had menstruated at that time. (The younger age groups have been omitted, since they are not relevant.) The corresponding percentages for the English control series and for Wilson and Sutherland's six Oxfordshire schools are given for comparison.

The median age of menarche in the second Nigerian series is 14.40 years. Although the numbers are small, this provides general confirmation of the findings in the first

TABLE II.—*Percentage of Children who have Reached Menarche at Each Successive Birthday*

Age	2nd Nigerian Series		English Control Series (Ellis, 1947)	6 Oxfordshire Schools (Wilson and Sutherland, 1949)
	No.			
11	(142)	0	1·5	1·0
12	(131)	0	9·0	7·5
13	(101)	12·9	28·1	29·6
14	(67)	37·3	58·7	63·3
15	(46)	69·5	86·1	89·4
16	(21)	85·7	94·6	95·4
17	(7)	100	98·2	98·2

Nigerian series, in which the mean and median age of menarche is 14.22 years. It will also be seen that the percentages in the English control series correspond closely with those given by Wilson and Sutherland, in whose series the median age of menarche was 13.6 years.

The percentages of Nigerian girls graded as pubescent in each year of age are shown graphically in Fig. 2. From this, the median age at which 50% were non-pubescent and 50% pubescent was 11.15 years—i.e., approximately 3.25 years earlier than the median age of menarche as calculated on the whole series. Although the numbers in each yearly age group are too small to be very conclusive they suggest a long time-lag between the earliest appearance of breast tissue and the menarche, assuming that the older and younger girls in the series had been living under similar conditions. In this connexion, Hogben et al. (1948) calculated by a logistic formula on a series of English school-
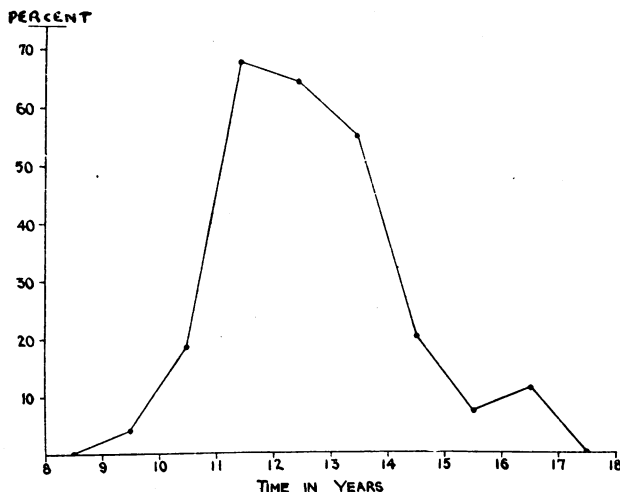

FIG. 2.—Percentage of Nigerian girls (second series) pubescent in each year of age.

girls that the age at which 50% were infantile with regard to breast development was 11.0±0.75 years, and with regard to menarche 13.6±0.77 years, a difference of 2.6 years.

Results in Boys

The percentages of boys graded as non-pubescent, pubescent, and adolescent in each year of age are shown in Table III, and the curves are compared in Figs. 3, 4, and 5.

TABLE III.—*Percentage of Boys Non-pubescent, Pubescent, and Adolescent in Each Year of Age*

Age Group (Years)	No.		% Non-pubescent		% Pubescent		% Adolescent	
	Nigeria	G.B.	Nigeria	G.B.	Nigeria	G.B.	Nigeria	G.B.
9–10	31	52	100	100	0	0	0	0
10–11	31	40	93·5	95	6·5	5·0	0	0
11–12	33	74	78·8	86·5	21·2	13·5	0	0
12–13	76	95	57·9	64·2	40·8	35·8	1·3	0
13–14	36	135	44·4	47·4	38·9	43·7	16·6	8·9
14–15	35	120	17·1	12·5	48·5	39·2	34·3	48·3
15–16	32	78	3·1	1·3	18·7	29·5	78·1	69·2
16–17	30	33	3·3	6·1	16·7	18·2	80·0	75·7
17–18	29	35	0	0	0	11·4	100	88·6

TABLE IV.—*Ages at which 75, 50, and 25% of Boys are Pubescent or More Mature*

% Pubescent or More Mature				Gt. Britain	Nigeria
75	..	..	..	..	14·14	14·10
50	..	..	..	..	13·14	12·95
25	..	..	..	..	12·15	11·80

It will be seen that the curves for Nigeria and Great Britain in Figs. 3–5 correspond more or less closely. In comparing the non-pubescent curves, it appeared best to take the median age (at which 50% of boys are non-pubescent and 50% pubescent or more mature), and also
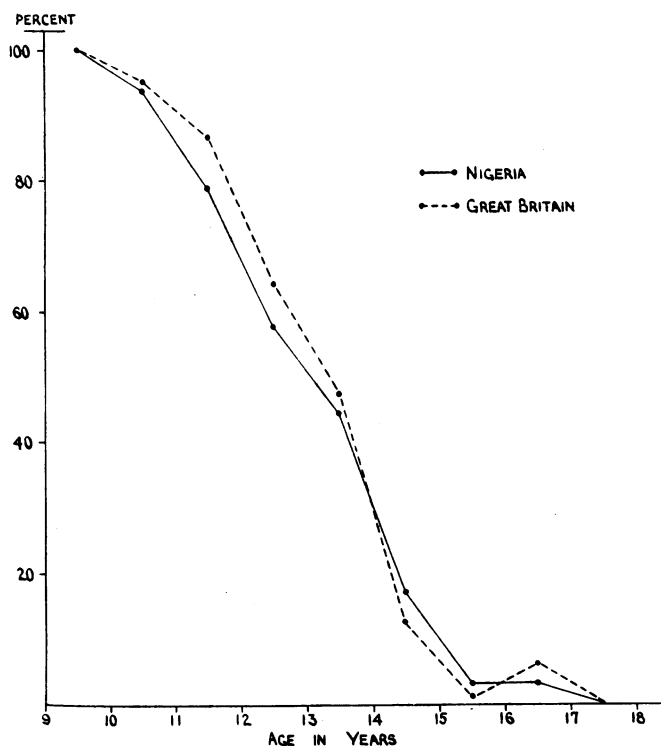
FIG. 3.—Percentage of boys non-pubescent in each year of age.

the ages at which 75 and 25% of boys are pubescent or more mature. The differences here are not statistically significant. There is also no significant difference between the two groups as regards the age at which adolescence is attained. In each case the median age is estimated at 15.0 years.

Summary and Conclusions

The above investigations lend no support to the belief that puberty occurs significantly earlier in tropical than in temperate climates. The mean age of menarche was found to be slightly but significantly later in Nigerian schoolgirls than in a control series in Great Britain. The mean age of menarche in this control series—13.73 years—may, in view of the regularity of the distribution curve, be compared with the median age of menarche of Oxford schoolgirls recorded by Wilson and Sutherland (1949), which was 13.6 years; a cross-check with a second series of Nigerian schoolgirls confirmed that the median age of menarche was later in Nigeria (14.4 years) than in Great Britain. The
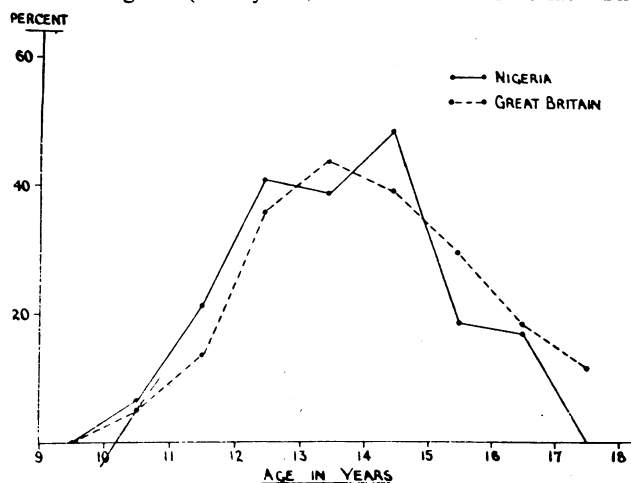

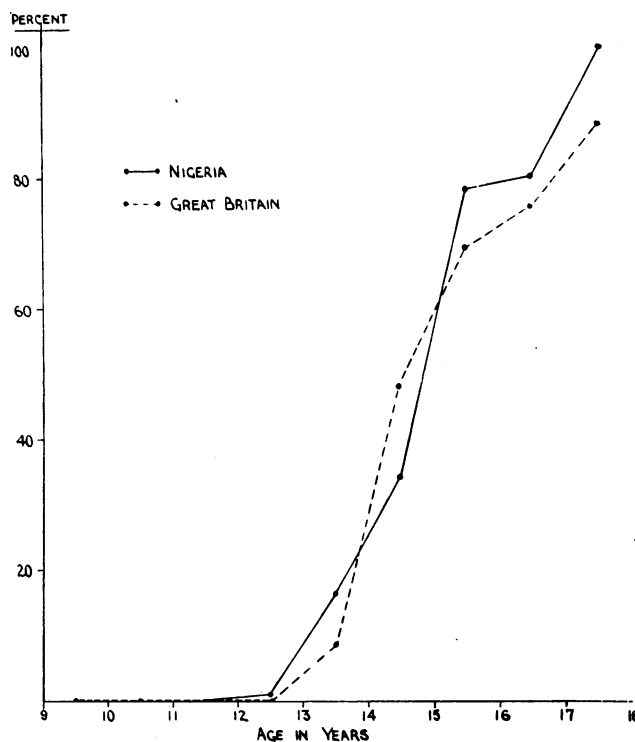FIG. 4.—Percentage of boys pubescent in each year of age.

FIG. 5.—Percentage of boys adolescent in each year of age.

degree of maturity of Nigerian schoolboys of different ages was essentially similar to controls examined in Great Britain. In so far as the social and economic background of the Nigerian children included in the survey was better than that of the general population of Southern Nigeria as a whole, puberty might be expected to occur earlier in the children studied than in those living under less favourable conditions. It is not suggested, however, that the Nigerian series and the controls are closely comparable as regards diet, environmental conditions other than climate, or incidence of infection, and it is not claimed that any differences which have or have not been observed are attributable to climate alone.

The observations have, however, some practical applications. Thus the age of consent for an unmarried girl in Nigeria is at present 13 years, as compared with 16 years in Great Britain, whereas the mean age of menarche provides no support for· this discrepancy. Nigerian law provides no protection against consummation of marriage before puberty, though a clear distinction should be drawn between "marriage by native law and custom," which is essentially a contract which may be made at any age, and consummation of marriage, which does not normally occur until after the menarche. Although native custom is strongly opposed to premature consummation of marriage, and it was in some tribes the custom for girls to enter a "fatting house" for one or more years after the menarche and before cohabiting with the husband, this prohibition is beginning to break down. With the drift to the towns, it is now not uncommon for children to reach the welfare officer in Lagos when marriage has been consummated before the menarche (Faulkner and Izzet—personal communication, 1949). Similarly, the Marriage Ordinance (as distinct from marriage by native law and custom) makes it possible for a child to be married at any age provided that the consent of her parents or guardian has been obtained. In a divorce case which recently came before the court, it appeared that marriage of a girl of 12 had

been effected by a Christian mission. While such cases are exceptional, they illustrate the danger of a belief in early maturity which appears to have no foundation in fact.

In the case of boys, legislation for the protection of juveniles in employment should be closely related to the expected development and physical performance at a given age (Ellis, 1948). In Nigeria this applies particularly to the minimum age at which boys may emigrate to Fernando Po for work in the plantations. In educational grouping and in defining regulations with regard to school-leaving age, it may well be borne in mind that adolescence is not likely to be reached significantly earlier in Nigeria than in Great Britain.

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THE PATHOLOGY OF HYPERSENSITIVITY REACTIONS IN MAN*

BY

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The title of this paper could have been "The Pathology of the Allergic Reactions in Man," but for reasons that will be evident later I consider it best to avoid the term "allergy." In his book on diseases of the liver Himsworth said of the term "cirrhosis" that it "not only misleads by implying an entity whose existence is doubtful, but has become so worn and defaced by loose usage as to have lost all precision." The same might well be said about the concept of allergy, which nowadays is used as a collective term for various forms of hypersensitivity. In characterizing a reaction as allergic we have said nothing about the precise nature of that reaction. For a better understanding of the character of allergic diseases, however, it will be necessary to distinguish between the various types of hypersensitivity reactions. I must therefore first give an introductory survey of the various forms of these reactions.

Anaphylactic Shock

A well-defined type of hypersensitivity is, as is well known, anaphylaxis. It is characterized by shock occurring when the antigen is injected into the circulation of the

sensitized animal and by an immediate cutaneous reaction with weal-formation if it is injected into the cutis. The serum of the sensitized animal is precipitated by the antigen, and it is possible to transfer this hypersensitivity passively from one animal to another. The most important symptoms of anaphylactic shock are contraction of the smooth muscles and dilatation of the capillaries and smaller blood vessels. An anaphylactic reaction can be produced by a single injection of the antigen provided the dose is so large that sufficient antigen is left in the organism to react with the antibodies after their formation A reaction of this kind often occurs in human subjects who have been injected with horse serum for therapeutic or prophylactic reasons. We call it serum sickness, and the symptoms are temporary pains in joints and muscles, temporary swelling of the joints, erythema, urticaria, purpura, angioneurotic oedema, etc.

If we sensitize an animal by repeated intracutaneous injections of the antigen at regular intervals the local reaction becomes stronger with every injection and finally the swelling ceases to disappear, haemorrhages and necrosis occur, and ulceration follows. This type of anaphylactic reaction is called Arthus's phenomenon. The haemorrhages are a sign of severe damage to the vessels, and necrosis is a result of this damage.

The same symptoms that characterize experimental anaphylaxis and serum sickness also occur in many hypersensitivity diseases in men. In American literature these diseases are often described as "atopic" hypersensitivity reactions. As is well known, the prototype of these is pollen hypersensitiveness. One of the most prominent symptoms of anaphylactic shock is the contraction of the smooth muscles of the bronchi, where it is accompanied by dyspnoea. This symptom occurs in atopic hypersensitivity in the form of asthma. Besides the temporary cutaneous symptoms of serum sickness more chronic skin reactions sometimes occur in the form of eczema, particularly in children with hypersensitivity to food.

The antigen can be introduced by inhalation, through the digestive tract, or through the skin. This hypersensitivity is also transferable, as may easily be demonstrated by the Prausnitz–Küstner reaction. If the antigen is injected into the cutis there is rapid weal-formation as in anaphylaxis.

Drug Hypersensitivity

A special group of hypersensitivity reactions are those induced by a great number of substances of various kinds that are covered by the diffuse term "drugs." Many of these substances are not antigenic in themselves but become so only after having been conjugated with an albumin within or outside the body. These substances bring about two kinds of sensitivity reactions. The first is very like the atopic, the second more like the bacterial hypersensitivity reaction, which will be treated in greater detail later.

In the first type the sensitizing occurs through the respiratory tract, the digestive tract, parenteral injection, or epicutaneously, and the symptoms are similar to those occurring in serum sickness or in the atopic hypersensitivity diseases. In spite of this, however, it is usually not possible to produce an immediate reaction in the skin in the form of weal-formation by injecting the drug. Neither is it possible to demonstrate the hypersensitiveness to drugs by the Prausnitz–Küstner phenomenon.

According to Chase the difference in this respect from the previously mentioned hypersensitivity reactions is due partly to the fact that the quantity of antibodies in the